

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Effectiveness and safety of oral sedation in adult patients undergoing dental procedures: protocol for a systematic review
<b>AUTHORS</b>	Araújo, Jimmy; Motta, Rogério; Bergamaschi, Cristiane; Guimaraes, Caio; Ramacciato, Juliana; de Andrade, Natalia Karol; Figueiró, Mabel; Lopes, Luciane

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Thomas Anthony Montagnese Case Western Reserve University School of Dental Medicine U.S.A.
<b>REVIEW RETURNED</b>	25-May-2017

<b>GENERAL COMMENTS</b>	Very thorough. Nicely done.
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<b>REVIEWER</b>	Mustafa Arslan Gazi University Medical Faculty, Department of Anaesthesiology and Reanimation, Ankara, Turkey
<b>REVIEW RETURNED</b>	09-Jun-2017

<b>GENERAL COMMENTS</b>	Well-written meta-analysis
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<b>REVIEWER</b>	Sadna Rajan Melbourne Dental School, The University of Melbourne, Australia
<b>REVIEW RETURNED</b>	18-Aug-2017

<b>GENERAL COMMENTS</b>	<p>General comments</p> <p>Please check spelling- UK English vs US English and grammar. The manuscript needs further editing.</p> <p>Title</p> <p>Good to specify in the title, the population by including the term 'adult'. Also as specified in your aims, the focus is on oral sedation only. Replacing 'conscious sedation' with 'oral sedation' is more specific.</p> <p>Abstract</p> <p>1)'Dental surgeons have doubts regarding the effectiveness and safety of drugs used for conscious sedation.'</p> <p>Please explain why and the evidence to support this statement.</p>
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	<p>2) In the 'Ethics and dissemination' section, comment on whether ethics is needed and how you plan on disseminating your results subsequently. This section is missing in the main manuscript.</p> <p>Strengths and limitations of this study  Page 4, line 10 '... pre, trans, post....'  Do you mean 'peri' or during treatment outcomes?</p> <p>Items 2 and 3, are generic to all systematic review and meta-analysis. Would you like to specify specific benefits i.e. providing summary of adverse effects and safety concerns for commonly used oral sedative drugs for conscious sedation in dentistry</p> <p>Introduction  The introduction is brief and general  Page 4, line 48 Good definition of conscious sedation.</p> <p>Page 5, line 15-18 Briefly include various routes for conscious sedation. Specify your reference to '...some drugs'</p> <p>Page 5, line 20. "...an interesting tool.'  The advantages listed make conscious sedation an invaluable adjunct with non-pharmacological behaviour management techniques rather than a tool</p> <p>Page5, line 22-25 Specify the drug interventions you are referring to.</p> <p>Page 5, line 28- 47  Would be good to provide a comprehensive review of benzodiazepines commonly used with success. Include potential risks and benefits, known adverse effects and guidelines/regulation to ensure patient safety. What about the documentations to safeguard clinician and patients?</p> <p>Related papers of interest,  Dionne RA, Yagiela JA, Coté CJ, Donaldson M, Edwards M, Greenblatt DJ, Haas D, Malviya S, Milgrom P, Moore PA, Shampaine G, Silverman M, Williams RL, Wilson S. Balancing efficacy and safety in the use of oral sedation in dental outpatients. J Am Dent Assoc. 2006 Apr;137(4):502-13</p> <p>Donaldson M, Gizzarelli G, Chanpong B. Oral sedation: a primer on anxiolysis for the adult patient. Anesth Prog. 2007 Fall;54(3):118-28</p> <p>Page 5, line 48-57  Specify '....a great variety of drugs'</p> <p>'....there are a few studies comparing their effectiveness and safety in adults'  Do you mean due to the paucity or limited studies available in the literature?</p> <p>" ...benzodiazepine and other drug intervention administered orally...'  Please specify what you mean by 'other drug interventions'. Was this method mentioned in the above section? Do you mean benzodiazepine in combination with other drugs? If so, these would need to be included in the review section above.</p>
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	<p>The safety aspects have not been covered which will link the importance of monitoring vital parameters during the dental procedures.</p> <p>Page 5, line 52-57 The aim could be in a separate section titled, either 'Objectives' and/or 'Review question', whichever your preference</p> <p>Materials and methods General comments: Too many headings and subheadings. Bold only headings, subheadings can be in italics.</p> <p>Eligibility criteria Page 6, line 30-35: Patients Will all other surgical dental procedures be excluded ie management of oral pathologies (ie mucocoele, small cysts)?</p> <p>Page 6, line 36-40: Interventions 'Studies that in at least one arm, include the use of conscious oral sedation orally with benzodiazepines or other drugs in selected adult patients and in the other arm, include placebo (same route as the comparator) or other treatment.'</p> <p>What about combination drugs, will these studies be excluded?</p> <p>Page 6, line 41: Outcomes Please provide details for the primary and secondary outcomes listed</p> <p>Page 6, line 48 Title is too brief. American English spelling used 'randomization'</p> <p>Search methods for primary studies- A more generic heading would be suitable to reduce the number of subheadings in this section. Would be easier to read if sections are in separate paragraphs instead.</p> <p>Page 7, line35 Suggested heading change to 'Study eligibility determination' 'Four reviewers (RM, CC, LL and NK), working in pairs, will independently screen potentially relevant all citations and abstracts based on the eligibility criteria and will apply the selection criteria.'</p> <p>Page 7, line 56-58 Please review sentence construction and spelling (US) 'The reviewers will use a standardised and pre-tested form to extract for data extraction with information on how to extract them.'</p> <p>Your abstract has a section on 'Ethics and dissemination', this is missing in your manuscript.</p>
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<b>REVIEWER</b>	Paul Brady Cork University Dental School and Hospital Ireland
<b>REVIEW RETURNED</b>	19-Aug-2017

<b>GENERAL COMMENTS</b>	<p>This is a protocol for a proposed systematic review looking at the effectiveness and safety of the use of conscious sedation in patients submitted to dental procedures:</p> <p>Oral sedation should be mentioned in the title as the review is looking specifically at oral sedation. The most common method for achieving conscious sedation in adult patients is intravenous sedation with the benzodiazepine midazolam. I do not agree that benzodiazepines are more commonly administered orally in dentistry. In the UK and Ireland, the intravenous route is more common. Attempting to achieve conscious sedation that is adequate for oral surgery procedures via the oral route is difficult. The problem is that there is individual variability with the dose required. It is almost impossible to titrate the drug safely orally. Absorption via the oral route is unpredictable and dependent on many factors such as gastric emptying. There is a danger of over sedating. Respiratory compromise is the most serious side effect of benzodiazepine sedation. There is no mention of respiratory compromise in the introduction. The methodology should have the incidence of hypoxemia as an outcome measure especially when the review is looking at safety. Measuring hypoxaemia via pulse oximetry is mandatory for conscious sedation. Amnesia is a very useful effect of benzodiazepines. It is not mentioned and I would have thought that it should be an outcome measure. Of the oral benzodiazepines, Temazepam is probably the most widely used. It should be mentioned in the protocol. As stated in the following reference document, there is a difference between oral pre medication and oral sedation. I would encourage the authors to read pg 15 of the document.</p> <p>The Dental Faculties of the Royal College of Surgeons and the Royal College of Anaesthetists, Standards for Conscious Sedation in the Provision of Dental Care, 2015</p> <p>The protocol mentions the inclusion of randomized control trials where a placebo is used. It would not be ethical to consent an anxious patient for conscious sedation and then give them a placebo.</p> <p>There are very significant differences in what is practiced with regard to conscious sedation in different countries. The authors need to become au fait with sedation as it is practiced in different areas of the world. Oral sedation may be the norm in South America but it is not in the UK in Ireland.</p> <p>My general impression is that this protocol needs a major revision to enable it to be applicable globally.</p>
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## VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Thomas Anthony Montagnese

Institution and Country: Case Western Reserve University School of Dental Medicine, U.S.A.

Competing Interests: None declared

Very thorough. Nicely done.

Thank you very much for your attention in dealing with our manuscript.

Reviewer: 2

Reviewer Name: Mustafa Arslan

Institution and Country: Gazi University Medical Faculty, Department of Anaesthesiology and Reanimation, Ankara, Turkey

Competing Interests: None declared

Comment: Well-written meta-analysis

Response: Thank you very much for evaluating our manuscript. We have made several modifications in the references section to accommodate all reviewers' suggestions.

Reviewer: 3

Reviewer Name: Sadna Rajan

Institution and Country: Melbourne Dental School, The University of Melbourne, Australia

Competing Interests: None declared

Dear Authors,

Thank you for an interesting systematic review protocol. An update on the effectiveness and safety in the use of oral sedation in adults is timely. There are some minor revisions required. Please find my comments attached (BMJ2017.pdf).

Thank you very much for evaluating our manuscript. All the reviewer's requests were taken into consideration and the authors have found them highly constructive and greatly enhanced the manuscript.

A) General comments

Please check spelling- UK English vs US English and grammar. The manuscript needs further editing. In title, good to specify in the title, the population by including the term 'adult'. Also as specified in your aims, the focus is on oral sedation only. Replacing 'conscious sedation' with 'oral sedation' is more specific.

Response: A translation specialist has reviewed the text, following the reviewer's suggestions. We have made the changes suggested to the title, which now reads "Effectiveness and safety of oral sedation in adult patients undergoing dental procedures: protocol for a systematic review. The authors sincerely hope that such modifications will suit the reviewer's request.

B) Abstract

1) Dental surgeons have doubts regarding the effectiveness and safety of drugs used for conscious sedation. Please explain why and the evidence to support this statement.'

Response: This information has been revised in benefit of clarity. The original sentence has been replaced by "The management of anxious patients undergoing dental procedures is still a challenge in clinical practice. Despite a wide variety of drugs for oral sedation for adults patients, there are relatively few systematic reviews that compare the effectiveness and safety of different drugs administered via this route".

2) In the 'Ethics and dissemination' section, comment on whether ethics is needed and how you plan on disseminating your results subsequently. This section is missing in the main manuscript.

Response: The authors have included the appropriate text for this section and it now reads: "The evidence gathered from this study should provide dental surgeons with systematic knowledge on the effectiveness and safety of oral sedation in adults requiring dental surgical procedures. This in turn should contribute towards the decision-making process in dental practice, minimizing the risks of anxiety and ineffective pain control in clinical procedures, as well as possible side effects. Ethics approval is not required in a protocol for a systematic review. The systematic review will be published in a peer-reviewed journal and presented at conferences".

C) Strengths and limitations of this study

Page 4, line 10 '..., pre, trans, post....' Do you mean 'peri' or during treatment outcomes?

Response: We have made modifications to this sentence in benefit of clarity. The authors sincerely hope that this is now to the reviewer's satisfaction.

Items 2 and 3, are generic to all systematic review and meta-analysis. Would you like to specify specific benefits i.e. providing summary of adverse effects and safety concerns for commonly used oral sedative drugs for conscious sedation in dentistry.

The authors have found this comment highly pertinent and modified the text accordingly. Thank you.

D) Introduction

The introduction is brief and general

Response: We have made considerable changes to the Introduction aiming at clarifying the purpose of the protocol. The authors sincerely hope that the reviewer will find them suitable.

Page 4, line 48 Good definition of conscious sedation.

Response: Thank you very much for this kind comment.

Page 5, line 15-18 Briefly include various routes for conscious sedation. Specify your reference to '...some drugs'

Page 5, line 20. "...an interesting tool.'

The advantages listed make conscious sedation an invaluable adjunct with non-pharmacological behaviour management techniques rather than a tool

Page5, line 22-25 Specify the drug interventions you are referring to.

Response: The sentences above have been modified to clarify the point raised by the reviewer. Thank you for your careful eye when revising this manuscript.

Page 5, line 28- 47 Would be good to provide a comprehensive review of benzodiazepines commonly used with success. Include potential risks and benefits, known adverse effects and guidelines/regulation to ensure patient safety. What about the documentations to safeguard clinician and patients?

Response: This has now been modified to include a comprehensive review of the most widely used benzodiazepines. The authors are grateful for this suggestion, as it has clearly made a positive impact on the text.

Related papers of interest,

Dionne RA, Yagiela JA, Coté CJ, Donaldson M, Edwards M, Greenblatt DJ, Haas D, Malviya S, Milgrom P, Moore PA, Shampaine G, Silverman M, Williams RL, Wilson S. Balancing efficacy and safety in the use of oral sedation in dental outpatients. J Am Dent Assoc. 2006 Apr;137(4):502-13  
Donaldson M, Gizzarelli G, Chanpong B. Oral sedation: a primer on anxiolysis for the adult patient. Anesth Prog. 2007 Fall;54(3):118-28

Many thanks for the suggestions. We have included these references in the manuscript.

Comment: Page 5, line 48-57

Specify ‘....a great variety of drugs’

‘....there are a few studies comparing their effectiveness and safety in adults’

Do you mean due to the paucity or limited studies available in the literature?

“ ...benzodiazepine and other drug intervention administered orally...’

Please specify what you mean by ‘other drug interventions’. Was this method mentioned in the above section? Do you mean benzodiazepine in combination with other drugs? If so, these would need to be included in the review section above.

The safety aspects have not been covered which will link the importance of monitoring vital parameters during the dental procedures.

Response: The sentences above have been modified to dissolve any ambiguity. Thank you for spotting this issue.

Comment: Page 5, line 52-57 The aim could be in a separate section titled, either ‘Objectives’ and/or ‘Review question’, whichever your preference

Response: The authors agree with this suggestion and have modified the text accordingly.

E) Materials and methods: Too many headings and subheadings. Bold only headings, subheadings can be in italics. Search methods for primary studies- A more generic heading would be suitable to reduce the number of subheadings in this section. Would be easier to read if sections are in separate paragraphs instead.

Response: We have modified headings and subheadings to reading fluency. The authors are hopeful that such modifications will have solved this problem.

Comment: Eligibility criteria (Page 6, line 30-35): patients will all other surgical dental procedures be excluded i.e. management of oral pathologies (i.e. mucocoele, small cysts)?

Response: We have modified this sentence to clarify this point. Thank you for point this out.

Comment: Page 6, line 36-40: Interventions 'Studies that in at least one arm, include the use of conscious oral sedation orally with benzodiazepines or other drugs in selected adult patients and in the other arm, include placebo (same route as the comparator) or other treatment.' What about combination drugs, will these studies be excluded?

Response: We have modified these sentences following the reviewer's suggestion.

Page 6, line 41: Outcomes (Please provide details for the primary and secondary outcomes listed).

Page 6, line 48 (Title is too brief. American English spelling used 'randomization').

Response: This has been expanded, as suggested. Thank you.

Page 7, line 35 Suggested heading change to 'Study eligibility determination'.

'Four reviewers (RM, CC, LL and NK), working in pairs, will independently screen potentially relevant all citations and abstracts based on the eligibility criteria and will apply the selection criteria.'

Page 7, line 56-58 Please review sentence construction and spelling (US)

'The reviewers will use a standardized and pre-tested form to extract for data extraction with information on how to extract them.'

Response: This sentence has been modified and the text reviewed by a language specialist.

Comment: Your abstract has a section on 'Ethics and dissemination', this is missing in your manuscript

Response: This section has been added to the manuscript following the reviewer's advice. Many thanks for your invaluable comments.

Reviewer: 4

Reviewer Name: Paul Brady

Institution and Country: Cork University Dental School and Hospital, Ireland

Competing Interests: None declared

This is a protocol for a proposed systematic review looking at the effectiveness and safety of the use of conscious sedation in patients submitted to dental procedures: Oral sedation should be mentioned in the title as the review is looking specifically at oral sedation.

Thank you very much for evaluating our manuscript. The term "oral sedation" has inserted in the title as requested.

a) The most common method for achieving conscious sedation in adult patients is intravenous sedation with the benzodiazepine midazolam. I do not agree that benzodiazepines are more commonly administered orally in dentistry. In the UK and Ireland, the intravenous route is more common. Attempting to achieve conscious sedation that is adequate for oral surgery procedures via the oral route is difficult. The problem is that there is individual variability with the dose required. It is almost impossible to titrate the drug safely orally. Absorption via the oral route is unpredictable and dependent on many factors such as gastric emptying. There is a danger of over sedating.

Response: Thank you very much for this comment. We have made modifications to the Introduction to direct the systematic review protocol to oral sedation, as well as the characterization that oral sedation is one of the possible methods for sedation in Dentistry. We have also made changes to the text to highlight the possible advantages, disadvantages, indications and limitations of oral sedation.



b) Respiratory compromise is the most serious side effect of benzodiazepine sedation. There is no mention of respiratory compromise in the introduction. The methodology should have the incidence of hypoxemia as an outcome measure especially when the review is looking at safety. Measuring hypoxaemia via pulse oximetry is mandatory for conscious sedation. Amnesia is a very useful effect of benzodiazepines. It is not mentioned and I would have thought that it should be an outcome measure.

Response: We made appropriate changes to the text to address this issue, as the authors fully agree with the reviewer. Thank you.

Comment: Of the oral benzodiazepines, temazepam is probably the most widely used. It should be mentioned in the protocol. As stated in the following reference document, there is a difference between oral pre medication and oral sedation. I would encourage the authors to read pg 15 of the document.

Response: We have included information on temazepam as well as the differentiation in definition between premedication and oral sedation, as kindly pointed out by the reviewer.

Comment: The Dental Faculties of the Royal College of Surgeons and the Royal College of Anaesthetists, Standards for Conscious Sedation in the Provision of Dental Care, 2015  
The protocol mentions the inclusion of randomized control trials where a placebo is used. It would not be ethical to consent an anxious patient for conscious sedation and then give them a placebo.

Response: We have included this type of study in order to evaluate the quality of evidence of possible studies relating to this topic, as, regrettably, there are several studies in literature using this type of design.

Comment: There are very significant differences in what is practiced with regard to conscious sedation in different countries. The authors need to become au fait with sedation as it is practiced in different areas of the world. Oral sedation may be the norm in South America but it is not in the UK in Ireland. My general impression is that this protocol needs a major revision to enable it to be applicable globally.

Response: We made substantial modification to the proposed protocol to address the issue raised by the reviewer, especially with regard to oral sedation as only one of the possible approaches to tackle anxious patients in dentistry. The authors sincerely hope that such changes will be to the reviewer's satisfaction.

## VERSION 2 – REVIEW

<b>REVIEWER</b>	Sadna Rajan The University of Melbourne, Australia
<b>REVIEW RETURNED</b>	26-Sep-2017

<b>GENERAL COMMENTS</b>	<p>Article no: bmjopen-2017-017681</p> <p>Title: Effectiveness and safety of oral sedation in adult patients undergoing dental procedures: protocol for a systematic review</p> <p>General comments: Thank you for addressing all the points highlighted. This protocol is suitable for publication in the present format. Some minor comments below:</p> <p>Spelling errors:</p> <p>Page 3, line 54. Replace 'adress' with 'address'</p> <p>Page 4, line 19. Replace 'de' with 'the'</p> <p>Page 7, line 43, 55. Replace 'standardized' with 'standardised'</p> <p>Page 8, line 9. Replace 'randomized' with 'randomised'</p> <p>Page 8, line 14. Replace 'characterization' with 'characterisation'</p> <p>Page 8, line 51. Replace 'categorized' with 'categorised'</p> <p>Eligibility criteria:</p> <p>Page 6, line 19. The term 'etc' is ambiguous, either include oral pathologies as a 'dental surgical interventions' or not.</p> <p>Discussion:</p> <p>Page 11, line 13. "....,such as exodontia and dental implants, ..."</p> <p>The types of 'dental surgical interventions' have been listed in the inclusion criteria section however only two have been highlighted here.</p>
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## VERSION 2 – AUTHOR RESPONSE

Reviewer: 3

General comments: Thank you for addressing all the points highlighted. This protocol is suitable for publication in the present format. Some minor comments below:

Spelling errors:

Page 3, line 54. Replace 'adress' with 'address'

Page 4, line 19. Replace 'de' with 'the'

Page 7, line 43, 55. Replace 'standardized' with 'standardised'

Page 8, line 9. Replace 'randomized' with 'randomised'

Page 8, line 14. Replace 'characterization' with 'characterisation'

Page 8, line 51. Replace 'categorized' with 'categorised'

Eligibility criteria:

Page 6, line 19. The term 'etc' is ambiguous, either include oral pathologies as a 'dental surgical interventions' or not.

Discussion:

Page 11, line 13. "....,such as exodontia and dental implants, ..."

Response: The types of 'dental surgical interventions' have been listed in the inclusion criteria section however only two have been highlighted here.

Thank you very much for the careful reading that has helped us to improve the manuscript. All adjustments and corrections are highlighted in the manuscript file.